Isotope Supply 2002 - 2010
University Supply, Accelerator Model

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National Cancer Institute (1 R24CA86307)

Initial targetry developmental work done in collaboration with Newton Scientific Inc., (DOE, DE-FG02-97ER82442)

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Washington
WASHINGTON UNIVERSITY IN ST LOUIS
MIR Mallinckrodt Institute of Radiology

NCI Sponsored Research Resource (R24 CA86307)

- Objectives
  - Production and distribution of nonstandard isotopes
    - Service
    - Collaborative
  - Access to WU facilities
    - microPET
      - characteristics of non-standard isotopes

A Research Resource in Radionuclide Research

- Characteristics of nuclides chosen for production
  - Determination of image quality
  - Determination of purity
- Production
  - Development of target systems
  - Development of purification methods
- Automation
  - Development of automation to improve production quality
  - To reduce personnel exposure

Nuclides Selected for Production

- Cu-60, Cu-61, Cu-64 - wide range of $t_{1/2}$

  Cu-64 has the potential for diagnosis and therapy

- I-124, Br-76, Br-77 - PET and therapeutic isotopes

  nuclides applicable to a wide range of compounds

- Tc-94m - PET Tc-nuclide

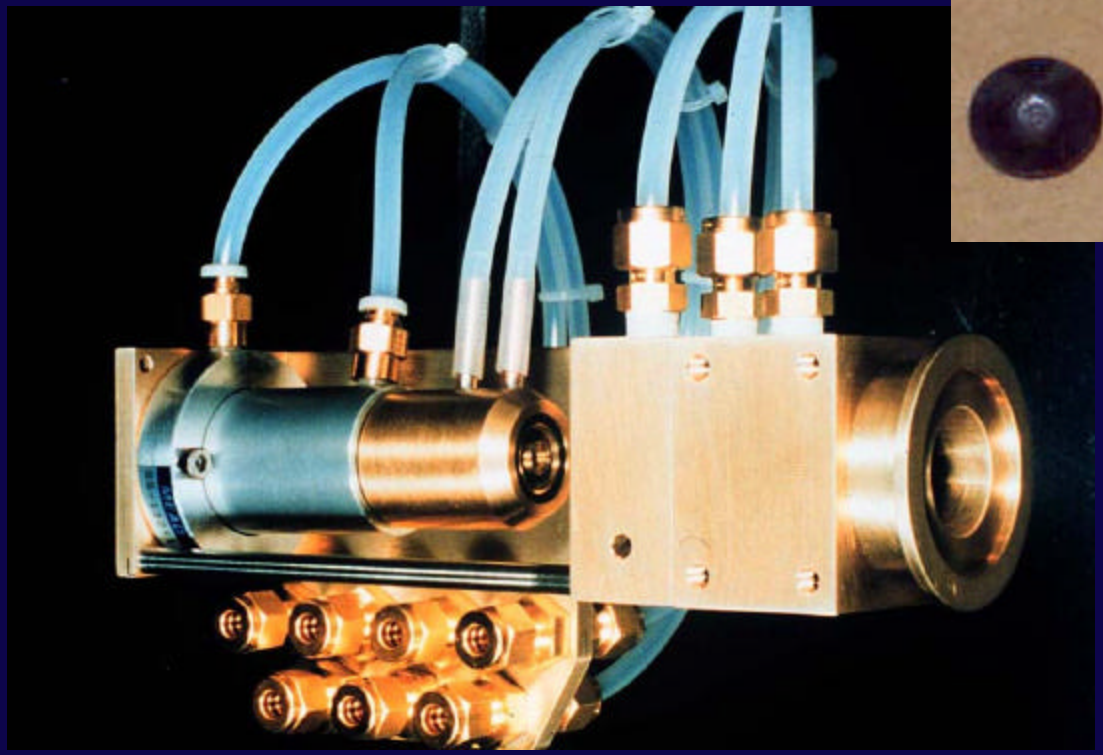
- Ga-66 - $t_{1/2}$ between Ga-68 and Ga-67

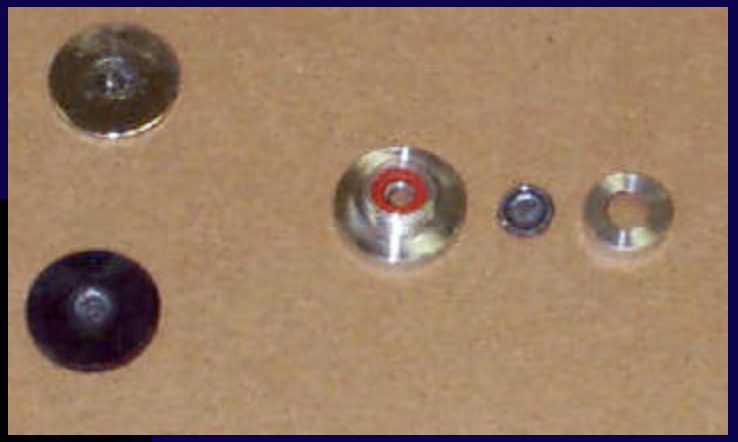
- Y-86 - potentially useful for dosimetry prior to Y-90 therapy

Characteristics of Nuclides Selected for Production

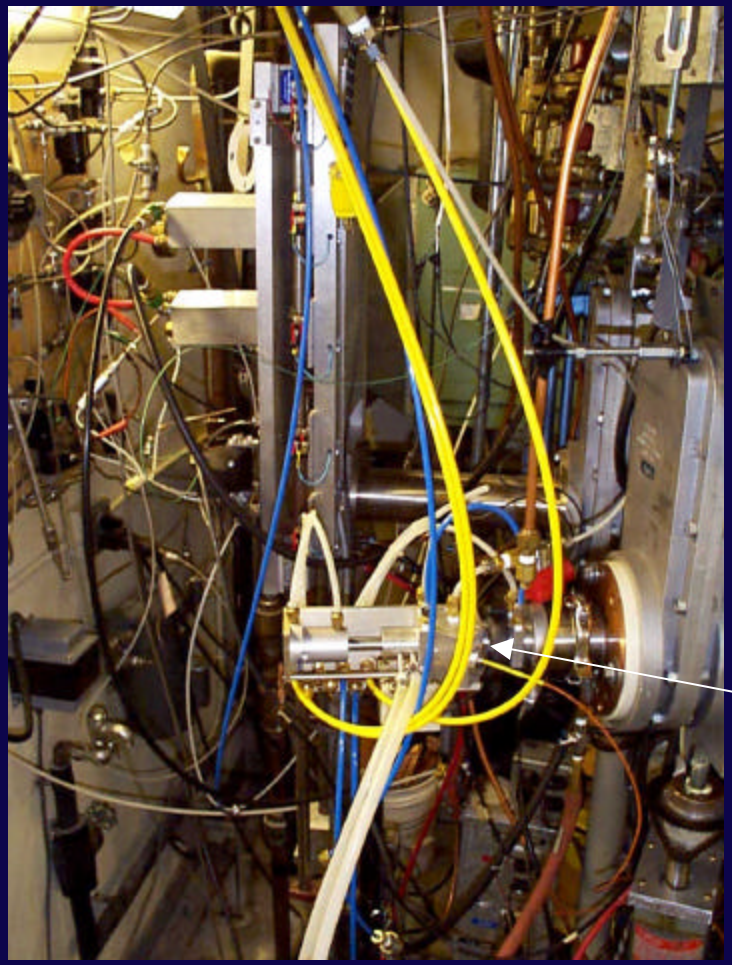
Isotope	Half-life	Decay modes/ %	Maximum β^+ energy (MeV)	Reaction	Natural abundance of target isotope
^{76}Br	16.2 h	β^+/57.0 EC/43.0	3.98	^{76}Se(p,n)	9.1%
^{77}Br	2.4 d	β^+/0.74 EC/99.3	0.36	^{77}Se(p,n)	7.6%
^{124}I	4.18 d	β^+/25.0 EC/75.0	2.15	^{124}Te(p,n)	4.8%
^{86}Y	14.74 h	β^+/34.0 EC/66.0	3.15	^{86}Sr(p,n)	9.9%
^{94m}Tc	52.0 m	β^+/72.0 EC/28.0	2.47	^{94}Mo(p,n)	9.3%
^{66}Ga	9.49 h	β^+/56.5 EC/43.5	4.15	^{66}Zn(p,n)	27.8%
^{60}Cu	23.7 m	β^+/93.0 EC/7.0	3.92	^{60}Ni(p,n)	26.1%
^{61}Cu	3.32 h	β^+/60.0 EC/7.0	1.22	^{61}Ni(p,n)	1.25%
^{64}Cu	12.7 h	β^+/19.0 EC/43.0 β^-/38	0.66	^{64}Ni(p,n)	1.16%

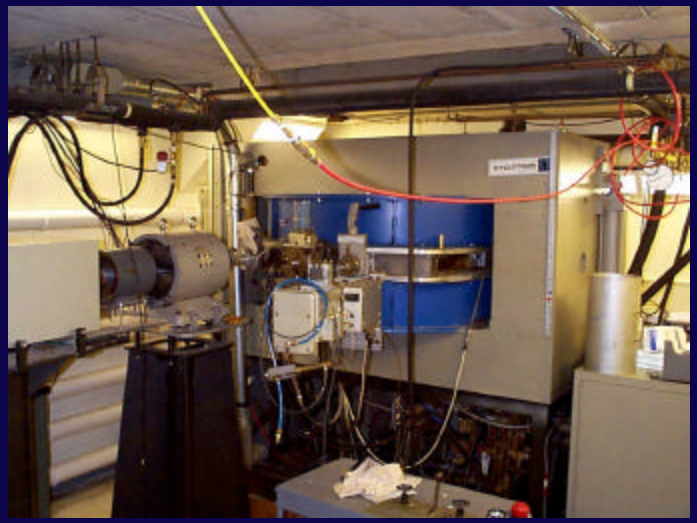
Targetry

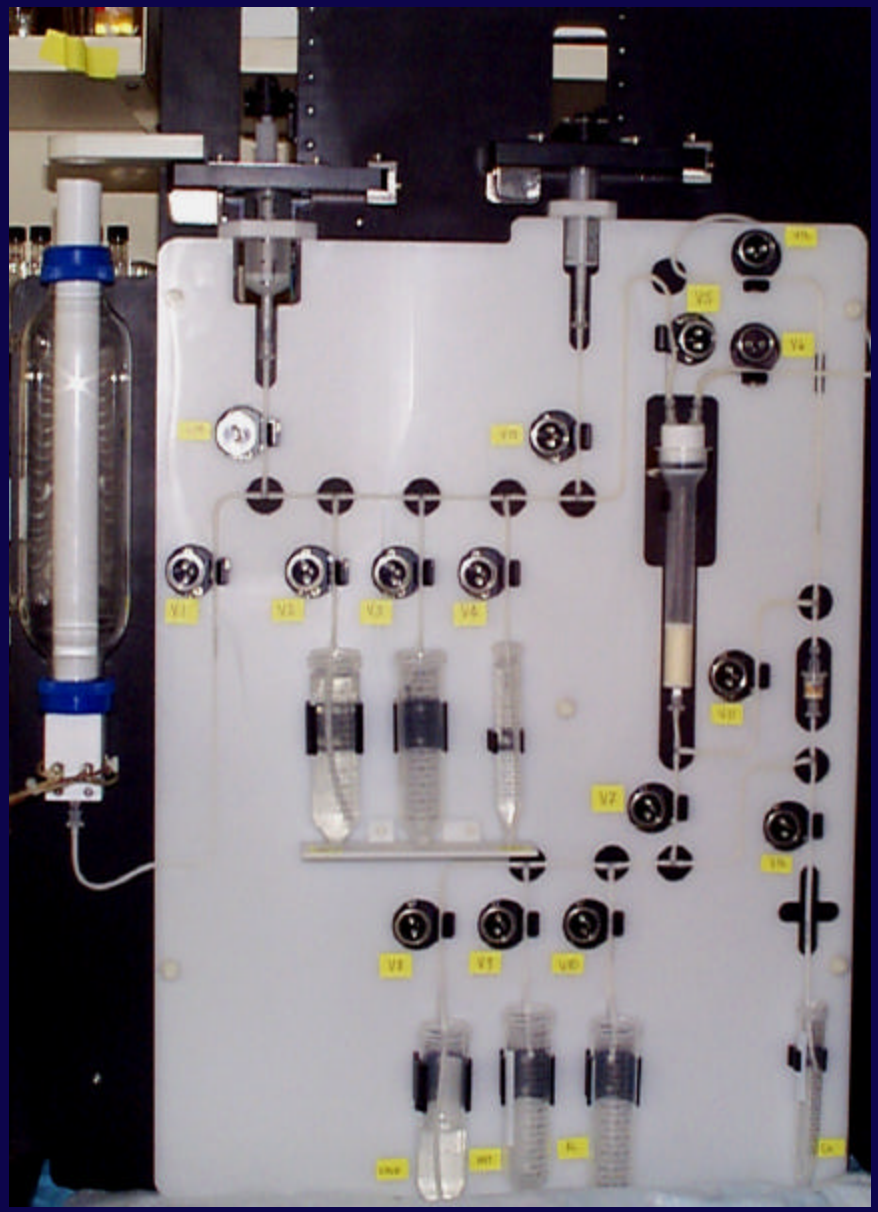




CS-15 Cyclotron and Target Stations







Automated processing system for Cu isotopes

Cu-64 Production

year	mCi of Cu-64	# productions
1995	2519	14
1996	4242	29
1997	5626	37
1998	7924	41
1999	10375	35
2000	11867	51
2001	12003	48
2002 (feb)	2121	6
Total	56677	256

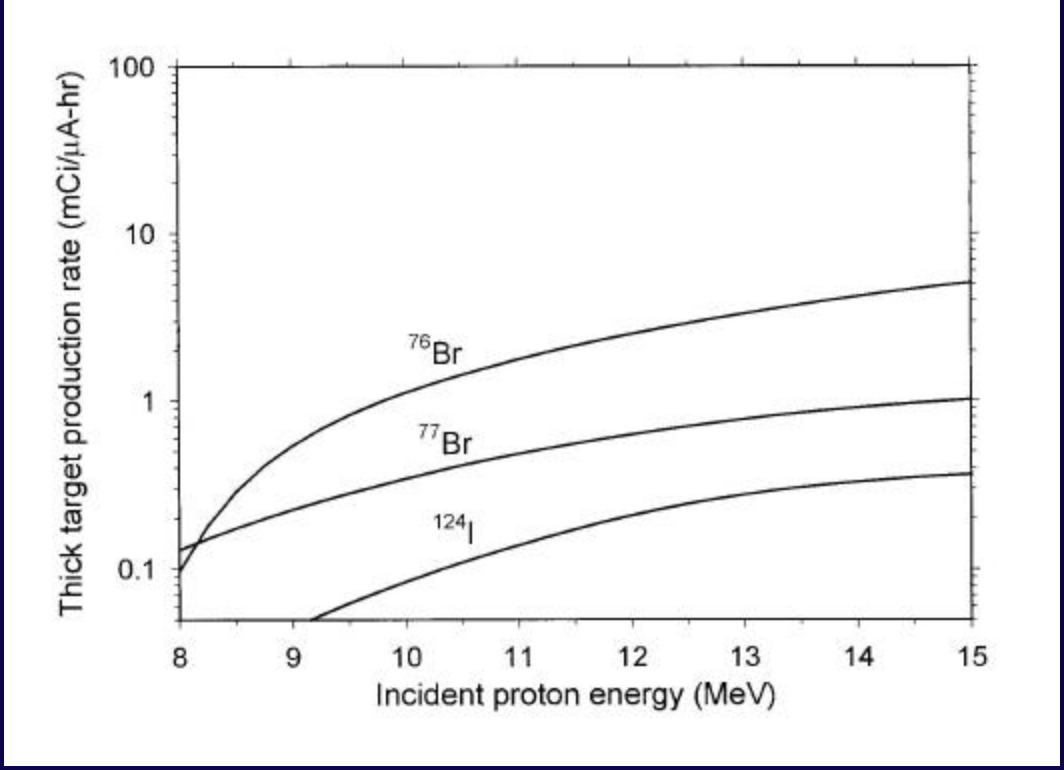
Production of Cu-60 and Cu-61

	2000		2001		Total	
	# productions	mCi	# productions	mCi	productions (since 1996)	mCi
Cu-60	35	5094	32	4386	121	34466
Cu-61	6	1051	2	443	26	3172

Bromine & Iodine Isotopes for Imaging and Therapy

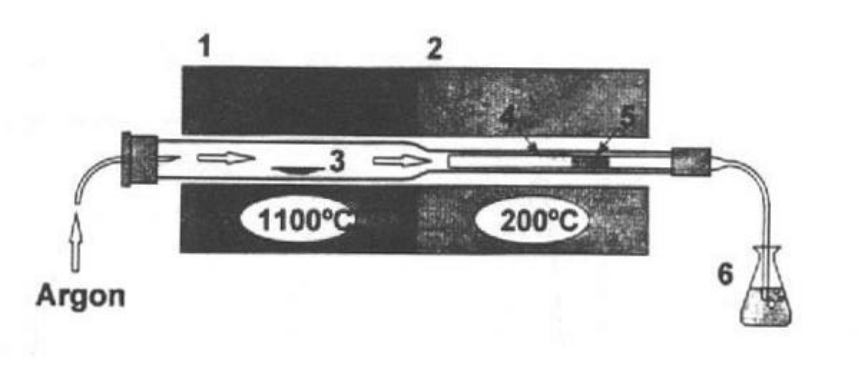
^{76}Br 16.2 hr	57% ß$^{+}$ (18 mm positron range) 43% EC 0.68 Auger e^{-}/decay	3.98 MeV
^{77}Br 2.4 d	0.74% ß$^{+}$ (0.2 mm positron range) 99.3% EC 0.85 Conversion e^{-}/decay	0.36 MeV
^{124}I 4.2 d	25% ß$^{+}$ (10 mm positron range) 75% EC 0.713 Auger e^{-}/decay	2.14 MeV

Thick Target Production Yields



Calculated from published cross-sections and using SRIM-96 (for proton stopping power in target material)

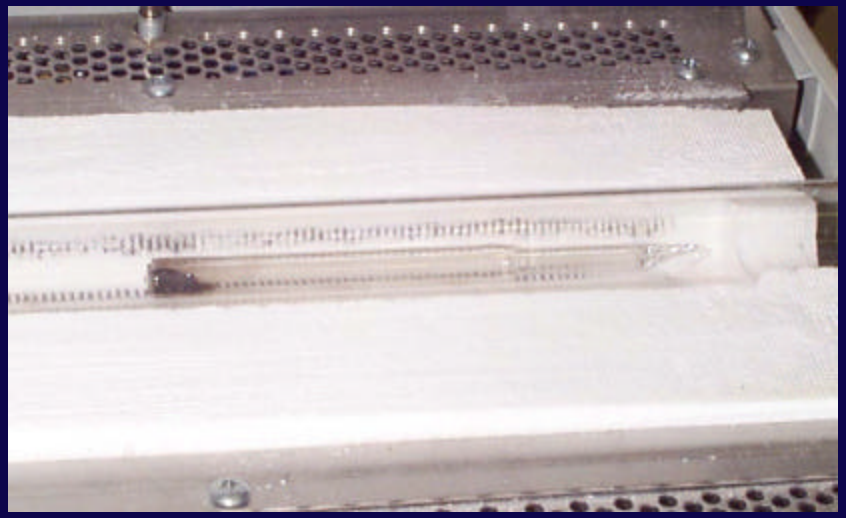
Removal of Radioactivity from Target

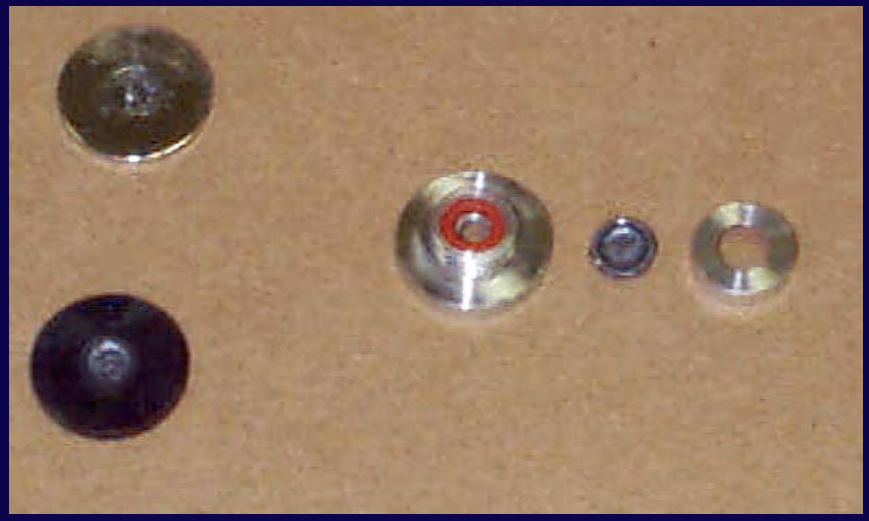


Dry distillation technique

Tolmachev *et al. Appl. Rad. Isot.* **49**, 1537-1540 (1998)

Preparation of $Cu_2{}^{76}Se$, $Cu_2{}^{77}Se$ & $Cu_2{}^{124}Te$

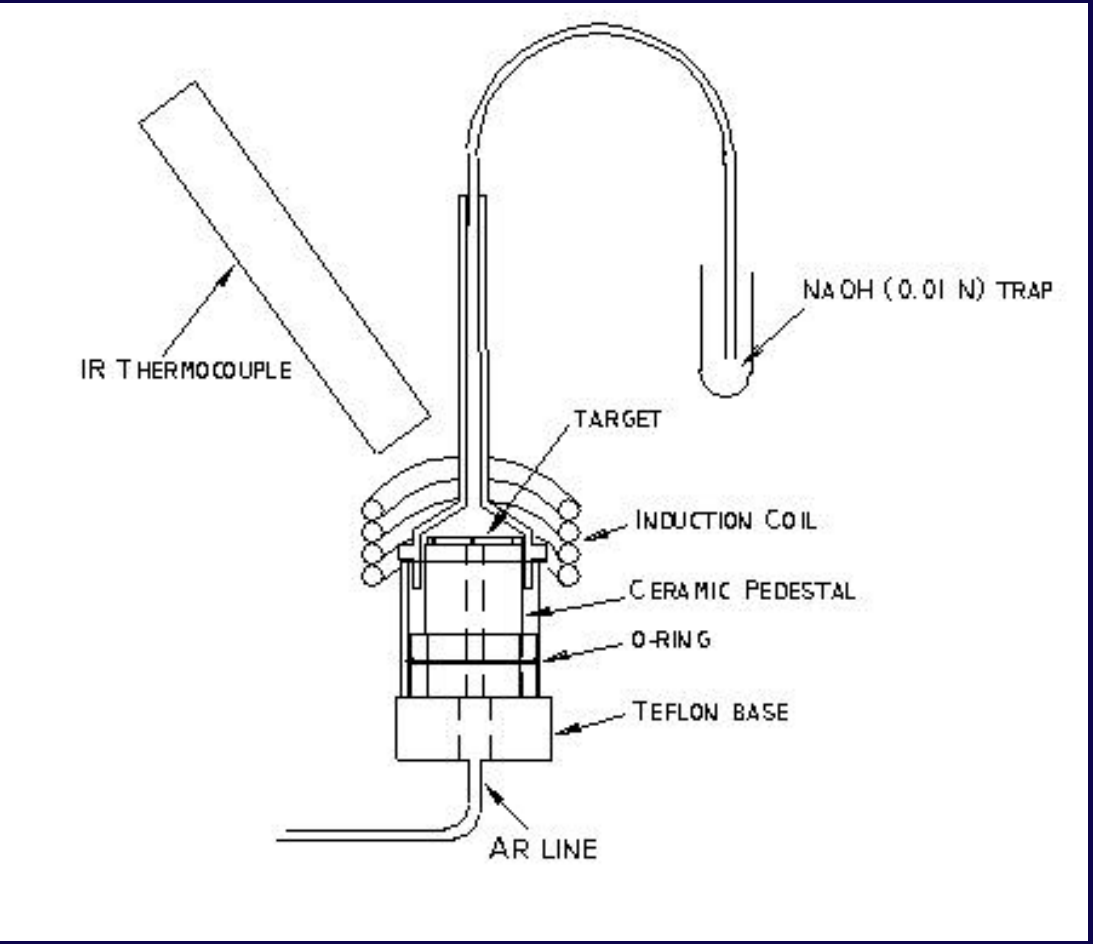




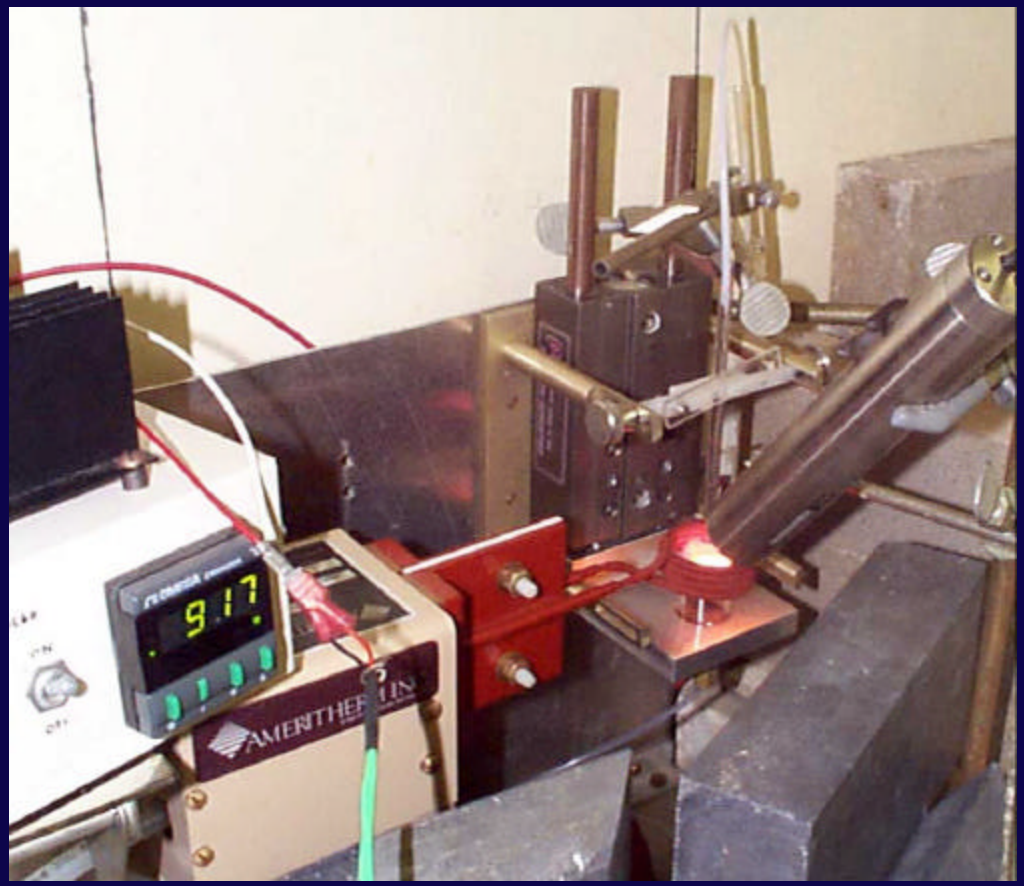
Combined stoichiometric amounts of copper and enriched selenium (or tellurium) in an evacuated quartz ampoule. Heated at 400-500 C for 6-10 days.

50-60 mg then placed into target depression, pressed and melted.

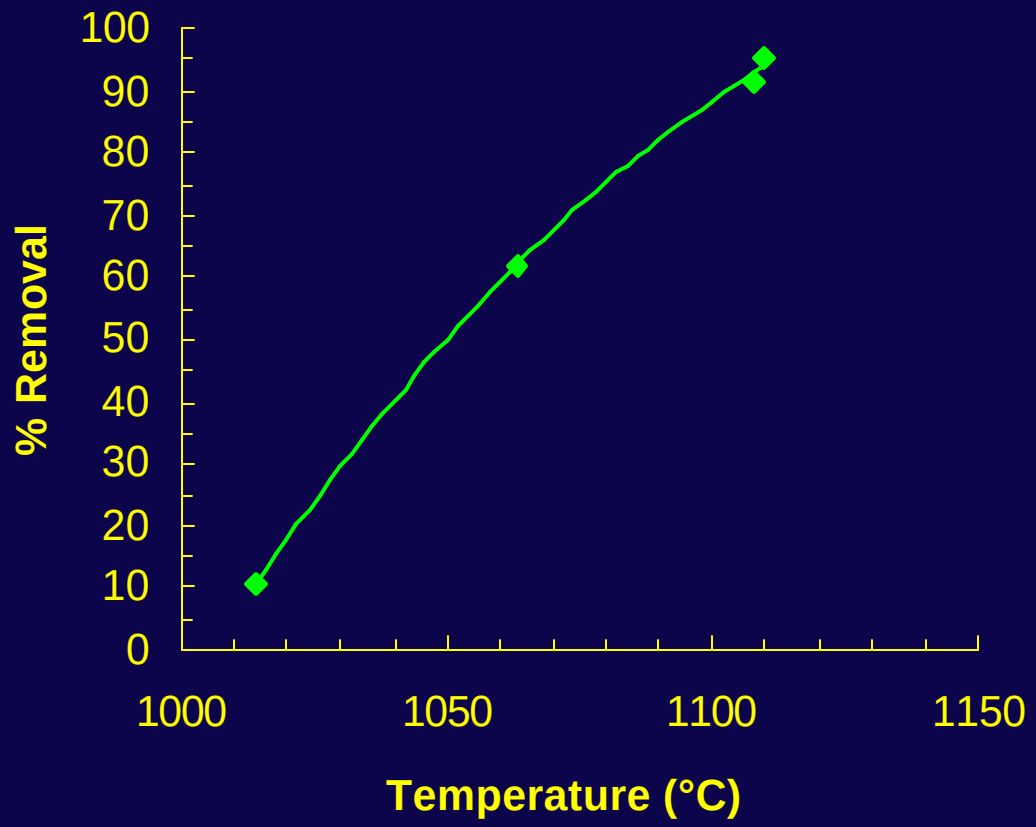
Washington University Induction Furnace Set-up



Induction Furnace Set-up



Recovery as a Function of Temperature



^{76}Br Activity removal in 10 min distillation - Pt Disk

Halogen Targetry - Production Yields

Isotope	Production Yield (mCi/mAh)		Thickness (mg/cm^2)
	Measured	Predicted	
Br-76	2.4	2.5	160
Br-77	0.89	0.94	221
I-124*	0.25	0.26	203

* beam degraded (to 12.5 MeV) by aluminum foil (0.44mm)

Shipping

- 12/97 to present: 427 shipments, 257 Limited Quantity (2.4 mCi) and 170 standard (up to 100 mCi). Total activity shipped 6646 mCi
- Activity shipped since RR: 378 shipments, 222 Limited Quantity, 156 standard. Total activity shipped is 5747 mCi.
- Shipped to 19 institutions.
- Inter-institutional contract required for greater than Limited Quantity amounts (10 institutions).
- DOT trained personnel for packaging and shipping (FEDEX).
- Obtained DOT approved packaging material.
- Have shipped limited quantities of ^{76}Br.

Shipping (projects)

- Purdue, Mark Green - ^{64}Cu-labeled folate chelate conjugates. Imaging and therapy of folate receptor positive ovarian carcinomas.
- USDA, Philip Reeves - Effect of dietary Zinc levels on the absorption of Cu. Uptake, transport and mechanism.
- U of Michigan, Dennis Thiele - Structural and functional analysis of eukaryotic copper transporters.
- UAB, Buck Rogers - ^{64}Cu-labeled bombesin analogue for imaging tumors with gastrin releasing peptide receptors (GRPr).
- CSU, Fullerton, Maria Linder - (1) Delivery of copper to mammary gland and milk and the effects of lactation in rats. (2) Evaluation of Cu binding affinity of rat and human serum macroglobulins.
- Harvard, Alan Packard - Functional imaging of MDR with PET

Shipping (projects)

- Harvard, Eva Barbarics/Alun Jones- ^{64}Cu-labeled isonitrile complexes with varying lipophilic character to enhance the tumor-cell accumulation in chemotherapeutically sensitive and resistant human breast-tumor-cell cultures.
- Temple University, Linda Knight - Evaluation of ^{64}Cu-labeled Bitistatin for targeting integrins in tumor angiogenesis with PET
- UCLA, Sam Gambhir - Ex Vivo cell labeling with ^{64}Cu-PTSM for imaging cell trafficking in mice with PET
- COH/UCLA, Anna Wu, Sam Gambhir - Copper-64-labeled engineered antibody fragments for PET imaging and therapy
- Fox Chase, Donald Chapman - Preclinical evaluation of azomycin-cyclams as markers of tumor hypoxia and radioresistance

Washington University Collaborations

- Jonathan Gitlin - Evaluation of the physiological role of copper in neurodegenerative disease
- Jim Wang - In vivo imaging of experimental acute autoimmune uveitis. In vivo imaging of adoptive immunotherapy: the CMS5/DUC18 Tumor ablation Model
- Eduardo Moros/Robert Myerson - Effects of mild hyperthermia on the oxygenation of tumor tissue for the enhancement of tumor sensitivity
- Jason Lewis - Evaluation of ^{64}Cu-ATSM for radiotherapy
- Carolyn Anderson - Cu-64 labeled antibodies and peptides for therapy
- Steven Weintraub - Role of bcl-x in tumor progression and tumor sensitivity to antineoplastic agents

Collaborations involving Tc-94m, Br-76, Br-77 and Ga-66

- Purdue, Mark Green - Ga-66 Folate imaging
- Washington University, Yvette Sheline and Mark Mintun - Br-76, I-124 agents to study neurogenesis
- Washington University, David Piwnica-Worms - Tc-94m sestamibi for MDR
- University of Illinois, John Katzenellenbogen - Tc-94m labeled Tricarbonyl organometallics. Br-76, Br-77 and I-124 labeled steroids for imaging and therapy of receptor-positive tumors of the breast and prostate.

Select Publications

Hamaza, I., Faisst, A., Prohaska, J., Chen, J., Gruss, P. and Gitlin, J.D.: The metallochaperone Atox1 plays a critical role in perinatal copper homeostasis. Proceedings of the National Academy of Sciences, 98(12): 6848, 2001.

Lewis, J.S., Laforest, R., Buettner, T.L., Song, S-K., Fujibayashi, Y., Connett, J.M. and Welch, M.J.: Copper-64-diacetyl-*bis*(N^4-methylsemicarbazone): An agent for radiotherapy. Proceedings of the National Academy of Sciences, 98(3): 1206, 2001.

Wu, A.M., Yazaki, P.J., Tsai, S-W., Nguyen, K., Anderson, A-L., McCarthy, D.W., Welch, M.J., Shively, J.E., Williams, L.E., Raubitschek, A.A., Wong, J.Y.C., Toyokuni, T., Phelps, M.E. and Gambhir, S.S.: High-resolution microPET imaging of carcinoembryonic antigen (CEA)-positive xenografts using a copper-64 labeled engineered antibody fragment. Proceedings of the National Academy of Sciences, 97(15): 8495, 2000.

Select Publications (continued)

Adonai, N., Nguyen, K.N., Walsh, J., Iyer, M., Toyokuni, T., Phelps, M.E., *et al*. Ex vivo cell labeling with ^{64}Cu-pyruvaldehyde-bis (N^4-methylthiosemi-carbazone) for imaging cell trafficking in mice with positron-emission tomography. Proceedings of the National Academy of Sciences 99(5):3030, 2002.

Wipke, B.T., Wang, Z., Kim, J., McCarthy, T.J. and Allen, P.M. Dynamic visualization of a joint-specific autoimmune response through positron emission tomography. Nature Immunology 366, 2002.

Lewis, J.S., Connett, J.M., Garbow, J.R., Buettner, T.L., Fujibayashi, Y., Fleshman, J.W. and Welch, M.J. Copper-64-pyruvaldehyde-bis(N^4-methyl-thiosemicarbazone) for the prevention of tumor growth at wound sites following laparoscopic surgery: monitoring therapy response with microPET and magnetic resonance imaging. Cancer Research 62:445, 2002.